ACTG Network Leadership Group Application Summary Information

The development of potent antiretroviral (ARV) drugs has led to dramatic reductions in disease progression and improved survival among HIV-1-infected persons in the developed world. Development of these drugs has been accelerated by the unique alliance of academic, government, and industry scientists, clinicians, regulatory agencies, and community advocates. The ACTG has been at the forefront of these efforts for nearly 20 years. These advances have gone hand-in-hand with an improved understanding of the virologic and immunologic basis of AIDS pathogenesis. Nevertheless, significant problems remain. Safer, cheaper, and more convenient drugs and drug combinations are needed to provide better treatment options for all HIV-infected persons, particularly those infected with drug-resistant HIV-1, women of child-bearing potential, and patients in need of treatment for co-infections such as tuberculosis or viral hepatitis.

The work accomplished by the ACTG has had a profound impact on the well-being of persons infected with HIV-1. Clinical trials and laboratory studies conducted by the ACTG have made major contributions to optimizing antiretroviral therapy (ART), managing drug resistance, preventing and treating co-infections, evaluating acute and long-term toxicities, and demonstrating the importance of pharmacogenomics in predicting drug toxicities. Results of these studies have helped establish the paradigm for the management of HIV disease and form the basis of current treatment guidelines. This progress in the treatment of HIV-1-infected individuals has resulted in dramatic reductions in AIDS mortality in the U.S. and other countries of the developed world. Nevertheless, significant problems remain. Durable virus suppression is not achieved in a significant proportion of patients for a variety of reasons, including drug resistance, poor adherence, drug toxicity, pharmacokinetic and/or pharmacodynamic factors, and other host factors such as pretreatment plasma HIV-1 RNA levels and CD4+ lymphocyte count. Moreover, therapies for co-infections are often limited by poor efficacy, toxicity, drug-drug interactions, resistance, and cost. As better tolerated, more compact regimens for HIV-1 infection and co-infecting pathogens are developed, it is essential that they be evaluated through rigorously conducted clinical trials to inform treatment guidelines and establish evidence-based standards of care for HIV-1-infected persons.

A. Mission

The mission of the ACTG is to develop and conduct scientifically rigorous translational research and therapeutic clinical trials to (1) investigate the viral and immune pathogenesis of HIV-1 infection and its complications; (2) evaluate novel therapeutic agents and the most effective approaches and strategies for the use of existing agents to treat HIV-1 infection; (3) evaluate interventions and strategies to treat and prevent HIV-related opportunistic infections, co-infections, complications of therapies, and other HIV-1-related co-morbidities, and (4) publish and disseminate the findings from these studies to improve clinical care, prevent or delay HIV disease progression, and reduce or eliminate the morbidity and mortality associated with HIV-1 infection and its associated complications. Since its inception, the ACTG has conducted a wide range of clinical and laboratory studies that have resulted in numerous major insights that form the cornerstones of the current guidelines and standards of clinical management of HIV-1 infection and its co-morbidities and complications. The ACTG has re-configured its Network structure and function and is now poised to meet the challenges of future scientific needs to develop and evaluate increasingly successful HIV-1 treatment options and strategies for prevention of HIV-1 infection, and identify those most appropriate to implement on a global scale as the HIV epidemic continues to evolve in both resource-limited and resource-rich parts of the world. The scientific agenda and research plan proposed in this application build on the myriad past accomplishments of the ACTG to propose further development of innovative, hypothesis-driven, pathogenesis-based, and clinically-oriented studies of the treatment and prevention of HIV-1 infection and its sequelae.

B. Research Plan

The ACTG has developed a broad and comprehensive scientific agenda that it will undertake in collaboration with several key partners, including the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network, the HIV Vaccine Trials Network (HVTN), the HIV Vaccine Prevention Trials Network (HPTN), the Microbicide Trials Network (MTN), and others. We will conduct studies in five of the priority areas outlined under this RFA: (1) Translational Research and Drug Development, (2) Optimization of

Clinical Management, Including Co-Infection and Co-Morbidities, (3) Vaccine Research and Development, (4) Prevention of Mother-to-Child Transmission, and (5) Prevention of HIV Infection. This research agenda will be expanded to include oral health in collaboration with investigators supported by the National Institute of Dental and Craniofacial Research (NIDCR). An integrated Network Core Laboratory provides critical support to all aspects of the ACTG clinical and translational research program.

B.1 Translational Research/Drug Development

The ACTG proposes a broad scientific agenda to evaluate novel compounds for the treatment of HIV-1 infection and related co-infecting pathogens, and to further our understanding of HIV-1 pathogenesis. Twenty five percent of the ACTG's resources will be devoted to this priority area. Given the rapid progress in the field, it is difficult to predict in detail which new drugs, what new technologies, or what new discoveries in pathogenesis will shape the approach to ART 5 years from now. The clinical and laboratory studies proposed for implementation at the present time are offered as examples of the scientific and clinical expertise the ACTG brings to bear on the specific aims described above. However, it is understood that these goals will change as new knowledge is accumulated and as new scientific opportunities present themselves.

Specific Aims for Translational Research/Drug Development:

1. Evaluate anti-HIV compounds aimed at novel mechanisms of action/new targets, including small molecule entry inhibitors, uncoating inhibitors, integrase inhibitors and maturation inhibitors
2. Evaluate new classes of molecules with unique and improved features such as different resistance profiles and better pharmacologic or toxicologic properties
3. Evaluate new therapies for HIV-infected individuals with co-infections (e.g., tuberculosis, hepatitis C, malaria, and papillomavirus)
4. To integrate immune-based therapies in treatment regimens, emphasizing mechanisms of antiviral effect and immune reconstitution
5. Test new hypotheses generated by pathogenesis studies

The ACTG Network Laboratory will play a central role in these studies.

B.2 Optimization of Clinical Management and Co-Morbidities

The ACTG is dedicated to improving the lives of persons living with HIV/AIDS. To that end, we propose a bold therapeutic research agenda to optimize the clinical management of HIV disease. Initially 55% of ACTG resources will be devoted to this priority area. Highest priority is given to studies designed to optimize ART and the treatment of co-infections, with a particular focus on HIV-infected persons living in resource-poor countries. Additional priorities include developing new treatment paradigms that incorporate novel ARV agents and novel treatments for co-morbidities. Particular emphasis will be placed on strategies that allow for treatment simplification to promote adherence, minimize toxicity, and prevent drug resistance. Novel means of assessing and averting the risk of drug toxicities will be explored through collaborative studies with leading experts in pharmacogenomics. Coordination with investigators from other networks, including the Vaccine, Prevention, and Microbicide networks, will facilitate identification of acutely infected individuals for studies targeted at assessing the impact of early ARV therapy on viral set point and long-term outcome. Close integration of this research agenda with the ACTG Network Core Laboratories in Virology, Pharmacology, and Immunology and with the Human DNA Repository will provide access to the critical technologies and scientific expertise necessary to assess the effects of different treatment strategies on viral reservoirs and drug resistance, drug exposure and drug-drug interactions, HIV-1- and pathogen-specific immune responses, and human genomics. To accomplish these goals, the following specific aims are proposed:

Specific Aims for Optimization of Clinical Management, including Co-Morbidities:

1. Evaluate the effectiveness of new regimens, particularly those that incorporate agents with novel mechanisms of action or new treatment strategies.

2. Evaluate therapies and therapeutic strategies to provide safe and affordable therapies.
3. Optimize therapies on the basis of safety, adherence, resistance, durability of response, and prevention of transmission.
4. Evaluate long-term toxicities and the role of pharmacogenomics in predicting or managing toxicities.
5. Assess the role of early interventions in acutely infected individuals in modifying viral set point, and the impact of early interventions on long-term outcomes and transmission rates.
6. Evaluate the clinical effectiveness of strategies to provide safe and affordable therapies.
7. Study the pathogenesis of co-infections, complications related to ART, or progressive HIV disease such as malignancies, metabolic abnormalities, and other co-morbidities. Such research will be conducted with support from and in close collaboration with other NIH Institutes and other HIV/AIDS networks.

B.3 Vaccine Research and Development

In collaboration with the HVTN, the ACTG plans to undertake a limited series of studies designed to enhance HIV-1-specific immunity using a novel vaccines and adjuvants. In these studies, we will coordinate our work in the HIV-1-infected population in terms of both our selection of agents and assays for the assessment of HIV-1-specific immunity with parallel efforts of the HVTN in the HIV-1 seronegative population. These studies have two general scientific questions: (1) Can therapeutic interventions in HIV-1-infected individuals enhance key HIV-1 specific immune responses that contribute to control of viral replication in vivo? and (2) Can insights related to immune correlates of viral control obtained in therapeutic immunization studies provide guidance and direction to vaccine research programs in HIV-1 uninfected populations directed at preventing infection or ameliorating the course of HIV-1 disease?

Specific Aims for Vaccine Research and Development:

1. In collaboration with the HIV Vaccine Trials Network, to evaluate the immunogenicity and safety of selected candidate HIV-1 vaccines in HIV-1-infected individuals.
2. To elucidate correlates of immunologic control of viral replication in Phase IIb/III therapeutic vaccine trials.

B.4 Prevention of Mother-to-Child Transmission of HIV

Interventions designed to reduce or to prevent transmission of HIV-1 from mothers to their infants are undertaken in the context of lifelong infection of the mother and, potentially, in the child as well. Consequently, it is not possible to isolate issues related to the prevention of mother-to-child transmission from those related to the long-term implications of these interventions for the mother, her children and future children, and the larger community in which these efforts are undertaken. Accordingly, the ACTG has developed and implemented a comprehensive effort that is closely coordinated and integrated with those of the IMPAACT Network to address issues related to the health of HIV-1-infected women and their children over the course of their lives. To address these issues, the ACTG and the IMPAACT Network will work jointly to develop treatment options that prevent or minimize the development of drug-resistant strains of HIV-1 and that protect future treatment options to optimize outcomes for women and their children. This effort takes into account that women are exposed to antiretroviral drugs in the pre-, peri-, and post-partum periods and that antiviral interventions in any one of these periods has significant implications for the others. These efforts will be actively supported by the ACTG Core Virology Laboratory where specialized expertise in the detection and quantification of minority species variants will be critical to understanding the short- and long-term implications of the antiviral regimens used.

Specific Aims for Prevention of Mother-to-Child Transmission of HIV:

1. Develop options to prevent or minimize development of drug resistant strains of HIV-1 that would compromise clinical outcome and/or limit future treatment options.
2. Optimize drug regimens pre-, peri- and post-partum in resource-limited settings

B.5 Prevention of HIV-1 Infection

Taking advantage of the renewed emphasis on integrating HIV treatment with prevention in both clinical and research efforts, the ACTG will work collaboratively with investigators participating in the HPTN and the AIEDRP to conduct an integrated research program that seeks to develop approaches that can reduce the risk of transmission of HIV-1 to seronegative partners. This effort will include the development of strategies to identify, recruit, and retain individuals who are acutely infected and at particular risk for viral transmission for both biological and behavioral reasons, and the evaluation of novel approaches that include antiretroviral and behavioral interventions to prevent transmission. In studies that will be actively supported by the Network Core Virology and Immunology Laboratories, we will also undertake studies to evaluate the impact of ART—especially during periods of high levels of viral replication such as acute infection—on HIV-1 transmission risk, and to identify biological markers that predict the risk of transmission or acquisition of viral infection.

Specific Aims for Prevention of HIV Infection:

1. Develop approaches to identify, recruit, and retain individuals who are acutely infected with HIV-1 and have high viral loads, particularly in resource-limited settings.
2. Evaluate the impact of ART and other interventions on HIV transmission, especially when the intervention is initiated during acute infection when viral load is high; evaluate the impact of uptake and adherence to ART on HIV transmission and/or acquisition.
3. Evaluate biological markers and determine if those markers correlate with HIV transmission and/or acquisition.

B.6 Oral HIV/AIDS Research Alliance.

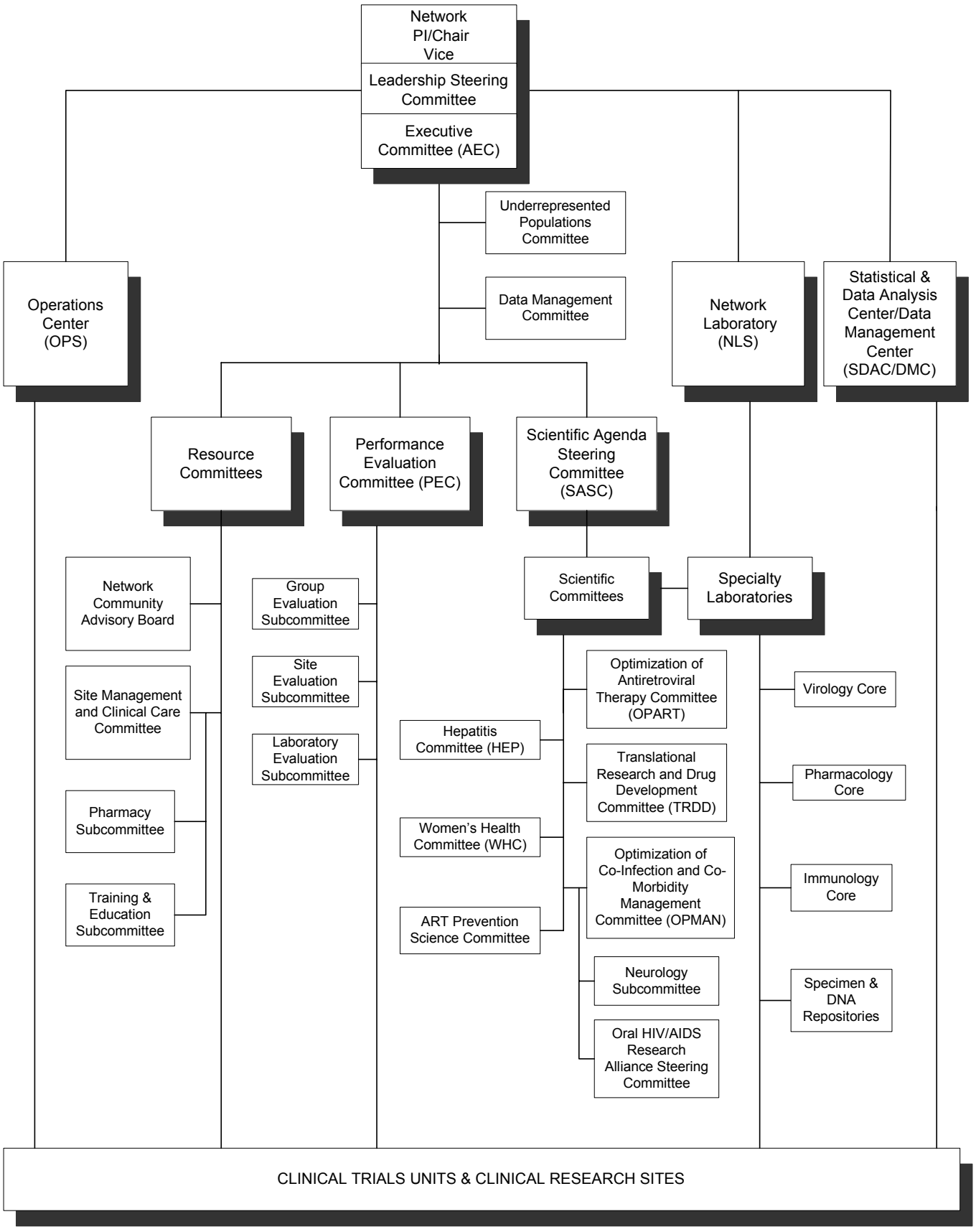
The ACTG will also include a comprehensive program in oral health that will be directed by a consortium of collaborating oral health centers supported by resources provided by the NIDCR. Three centers with an outstanding track-record in the conduct of oral HIV/AIDS research—Case Western Reserve University (CWRU), University of North Carolina (UNC), and University of California San Francisco (UCSF)—will collaborate to conduct multidisciplinary clinical trials in the United States and resource-limited settings aimed at optimizing clinical management of co-morbidities associated with AIDS that affect the oral cavity environment. The centers are directed by Mahmoud Ghannoum at CWRU, Caroline Shiboski at UCSF, and Jennifer Webster-Cyriaque at UNC. This collaboration will establish the Oral HIV/AIDS Research Alliance (OHARA), which will help to define the standard of care for AIDS-related oral opportunistic infection and disease by harnessing the extensive complementary resources available through the three centers and building strong alliances with the ACTG nationally and internationally. The OHARA alliance currently maintains collaborative research programs in four key sub-Saharan African countries (Kenya, Uganda, Malawi, Zimbabwe, South Africa) where oral manifestations of HIV infection—especially those related to neoplasia—are particularly severe. The OHARA alliance will establish an infrastructure capable of conducting research in domestic and international ACTG CRSs and develop a comprehensive research agenda focused on the pathogenesis and therapy of oral manifestations of HIV infection. The initial dual scientific foci of this effort will be oral candidiasis and oral AIDS-associated malignancies.

II. Key Personnel, Organizational Structure, and Coordination of the ACTG

The ACTG is directed by Dr. Constance Benson of the University of California, San Diego who serves as Principal Investigator and Chair of its Executive Committee. Dr. Daniel Kuritzkes of Harvard Medical School serves as Group Vice Chair. Dr. Robert Coombs of the University of Washington is the Director of ACTG Network Laboratories. The Network CORE Operations Center, located at Social & Scientific Systems, Inc. in Silver Spring, MD, is directed by Dr. Yvette Delph.

As shown in Figure 1, the organizational structure of the ACTG comprises the Network Leadership (which includes the Executive, Scientific and Resource Committees and the Coordinating and Operations Center [CORE]), the Network Laboratory (NL), the Statistical and Data Management Center (SDMC), and the Clinical Trials Units (CTUs) and their affiliated Clinical Research Sites (CRSs).

Figure 1. Organizational Structure of the ACTG Network



A.2 Scientific Committees

There are six major Scientific Committees of the ACTG representing the five specific areas of research focus of the Network. The Scientific Committees are the central scientific and protocol-generating bodies of the ACTG. They are responsible for developing, maintaining, advancing, and monitoring the scientific agenda and research plan of the Network and the conduct of the clinical trials within their purview; overseeing the analysis of study data; and ensuring the prompt dissemination of study findings through timely presentations and publications of their respective studies. The Scientific Committees develop comprehensive scientific research agendas and clinical trials to address those agendas that are consistent with the NIAID HIV therapeutic research agenda. They also interact with the NLs to integrate and coordinate laboratory research into the scientific agendas and protocols developed by the ACTG. The major Scientific Committees of the ACTG mirror five of the areas of investigation outlined in the Network RFA.

The Translational Research/Drug Development (TR/DD) Committee is responsible for the research plan related to the evaluation of new or novel antiretroviral or immune-based drugs, classes of drugs, or new therapies for the treatment of HIV and its complications, and for the testing of new hypotheses generated by pathogenesis studies.

The Optimization of Antiretroviral Therapy (OpART) Committee is responsible for the research agenda related to optimizing the management of antiretroviral therapies, including studies to evaluate the optimal use of new and novel drugs and classes of drugs in the context of existing antiretroviral therapies; for developing strategies to address prevention and management of toxicities and adverse effects of antiretroviral drugs, and for evaluating the short- and long-term outcomes of various antiretroviral treatment regimens and strategies, both in the U.S. and in resource-limited international settings.

The Optimization of Co-Infection and Co-Morbidity Management (OpMAN) Committee is responsible for the research agenda related to optimizing the management of co-infections and co-morbidities associated with HIV infection, including studies to evaluate the optimal approaches to treatment and prevention, both in the U.S. and in resource-limited international settings.

The Hepatitis Committee (HEP) is responsible for the research agenda related to the evaluation of new or novel compounds for the treatment of hepatitis B and C co-infection, and for optimizing the management of hepatic complications of antiretroviral therapies and the management of hepatitis B and C co-infections in the context of antiretroviral therapies both in the U.S. and in resource-poor international settings.

The Women's Health Committee (WHC) is responsible for the research agenda related to optimizing the treatment of HIV disease in women, the prevention and treatment of HIV-related complications in women, and understanding the pathogenesis of HIV disease and complications unique to HIV-1-infected women, including women from underrepresented populations in both the U.S. and in resource-limited international settings. The WHC chair and a subset of members of the WHC also participate in the recently formed joint IMPAACT-ACTG Women's Health and Perinatal Research Committee, which is responsible for research to optimize ART drug regimens pre-, peri- and post-partum for HIV-1-infected women at all stages of their disease. This Committee includes equal representation from both networks.

The ART Prevention Science Committee is responsible for the coordination of research activities with the proposed HPTN to integrate HIV treatment and prevention into the context of ACTG and HPTN clinical trials, including the evaluation of antiretroviral therapies for prevention of transmission, behavioral and therapeutic interventions to prevent or reduce transmission in the context of acute HIV infection, behavioral intervention strategies to prevent transmission in the context of therapeutic trials of chronically infected individuals, and approaches to evaluating the effectiveness of prevention strategies on public health.

A.3 Resource Committees

Resource Committees serve as the venues to identify and address specific functional roles and issues within the Network that pertain most directly to site and patient management and community outreach. Representatives of Resource Committees also participate in cross-Network activities to ensure effective coordination within the functional clinical research areas relevant to each Network. These committees include the following:

The Network Community Advisory Board (NCAB) (formerly the Community Constituency Group [CCG]) is a volunteer group of community representatives whose mission is to ensure that the views and concerns of

HIV-infected and affected individuals and populations most at risk are incorporated into the scientific and administrative priorities of the ACTG. The NCAB representatives are active participants in all Leadership and Scientific Committees and on all protocol teams of the ACTG.

The Site Management and Clinical Care Committee (SMCCC) oversees and resolves clinical research site operational, logistical, clinical care, and training issues essential for successful implementation and completion of the ACTG research agenda. The chair and vice chair of the SMCCC are Ms. Diane Daria and Ms. Tammy Powell, both of the University of Cincinnati Medical Center. The SMCCC provides: (1) advice and technical expertise in the areas of patient care, protocol implementation, and site operations; (2) training and education for site personnel at current and new research sites related to site management, protocol operation, collection of quality data, specimen collection and processing, regulatory issues, and organizing all other training and educational activities required by site staff who participate in the research effort (through the Training and Education Subcommittee; (3) site management support; (4) mechanisms to optimize the recruitment and retention of study subjects and educate site staff about strategies for recruitment and retention; (5) management of site and staff policies and procedures related to study drug acquisition, storage, shipment, dispensing, and training activities for site pharmacists (through the Pharmacy Subcommittee).

B. Coordinating and Operations Center (OPS)

The Coordinating and Operations Center of the ACTG is a component of Social & Scientific Systems, Inc. (SSS) in Silver Spring, MD, and is directed by Dr. Yvette Delph. SSS has served as the OPS for the ACTG since 1987. The OPS is the fiscal, administrative, and logistical management component of the Network.

C. ACTG Clinical Trials Units (CTUs) and Clinical Research Sites (CRSs)

ACTG-affiliated domestic and international CTUs and CRSs and their PIs/Site Leaders, co-investigators, and research staff are an integral part of the organizational and governing structure of the ACTG. The executive, scientific, and administrative leadership of the Network is drawn from the experienced investigators who have devoted their efforts to the basic, translational, and clinical investigation of important research questions in the field of HIV/AIDS. All policies, procedures, and key decisions made by the governing bodies of the ACTG are discussed in detail and developed with the input of the CTU and CRS investigators, personnel, and the patients and communities they serve. The PIs/Site Leaders are the voting members of the ACTG; as such, they elect the ACTG PI/Chair, Vice Chair, and key leaders in the governance structure, as defined in the process for selection of Executive, Scientific, and Resource Committee membership. The PIs/Site Leaders are responsible for implementing the research plans developed by the Scientific Committees and for conducting all ACTG protocols according to Good Clinical and Laboratory Practices and all other relevant regulatory requirements. The CTUs and CRSs:

- Provide the scientific expertise necessary to participate in the development of the scientific agenda and research plans.
- Provide the expertise to design and conduct clinical trials necessary to meet the scientific agenda.
- Accrue and retain the patient populations required for those trials.
- Have the personnel and facilities to conduct those trials in expert fashion.
- Provide the outreach and infrastructure support sufficient to recruit and retain in clinical trials the broad diversity of patients affected by HIV/AIDS, including women and underrepresented minorities.
- Provide the expertise from multiple medical and surgical specialties within their institutions necessary to obtain body tissues and perform therapeutic and diagnostic interventions.
- Provide the laboratory facilities to process, store, and ship to appropriate central laboratories blood, body fluids, and tissue samples obtained from clinical trial participants.
- Perform to the standards established by the network.
- Meet all regulatory requirements, including Institutional Review Board approval in a timely fashion.

D. ACTG International Program

During the current grant cycle, the ACTG made the expansion of its research agenda to resource-limited settings one of its highest scientific and operational priorities. The primary goal of the international ACTG program is to develop the capacity to conduct rigorous, state-of-the-art clinical trials designed to inform therapy in resource-limited settings disproportionately affected by HIV. We wish to continue to develop and to execute an array of clinical and translational studies that will create an evidence base by which to deliver optimal medical care to HIV-infected persons living in these areas. We have sought to broadly integrate international investigators within the fabric of the Network so that they can effectively use the resources and expertise of the Network to develop and execute a cross-cutting international and domestic agenda. We have established the sites with the view that they should ultimately function as free-standing programs that collaborate with domestic units. Through the efforts of international and U.S. investigators working together, the ACTG has developed a diverse menu of international studies that will focus on optimal management of the initial treatment of HIV in treatment-naïve individuals in resource limited settings (A5175), management of failures of NNRTI-based regimens (ACTG 5230), optimizing management of patients simultaneously presenting with active tuberculosis and HIV-1 infection (ACTG 5221), on non-amphotericin B-based management of cryptococcal meningitis (ACTG 5225), understanding the implications of single dose nevirapine interventions to prevent MTCT on subsequent NNRTI-based treatment regimens for women (A5208), and on a randomized trial using a novel factorial design to evaluate what drugs can best reduce NNRTI resistance selection in pregnant HIV-infected women and how long these various drugs should be continued in this setting (A5207). To conduct these studies the ACTG has established a total of 18 international clinical trials units around the world with the capability to conduct rigorous randomized therapeutic clinical trials according to Good Clinical Practice standards in the diverse international settings.

E. Network Core Laboratory

Clinical and translational research efforts of the ACTG will be actively supported by the ACTG Network Laboratories under the direction of Dr. Robert Coombs of the University of Washington. The NL consist of three Core Laboratories with specialized expertise in Virology, Pharmacology, and Immunology. As noted below, each Core Laboratory is composed of competitively selected Specialty Laboratories selected to provide the requisite breadth of laboratory expertise to support the comprehensive agenda of the ACTG and collaborating Networks. ACTG NL also includes a biological Specimen Repository at the Biomedical Research Institute (Rockville, MD) and a genomics repository at Vanderbilt University.

Network Core Virology Laboratory. The Core Virology Laboratory includes five specialty laboratories that provide the broad range of techniques and skills required by the ACTG's research agenda, including laboratories that have special expertise in the assessment of viral fitness and in HCV virology; the detection of minority species variants present in low copy number; the study of mechanisms and thresholds for drug resistance; in HCV and HBV virology, and; in viral compartmentalization and phylogenetic analysis of HIV. Virology Specialty Laboratories participate in the NIAID-sponsored Virology Quality Assurance Program to assure high-quality virology data from ACTG clinical trials.

Network Core Pharmacology Laboratory. The Core Pharmacology Laboratory includes four specialty laboratories with complementary areas of expertise in assays for new drugs and novel compounds, therapeutic drug monitoring, drug-drug interactions, non-compartmental and complex individual or population PK modeling and simulations, in cellular and tissue distribution of pharmacologic agents and the effects of protein binding, and in intracellular quantification. The Pharmacology Laboratory QA/QC Subcommittee oversees an extensive QA/QC program in which all laboratories are required to participate.

Network Core Immunology Laboratory. The Core Immunology Laboratory consists of five Specialty Laboratories with expertise in the assessment of response to vaccination and in the investigation of mechanisms of immunodeficiency, monitoring immune restoration following antiretroviral therapy, innate immunity, cellular and humoral immune responses to opportunistic pathogens, dendritic cells and CD8+ T-cell responses to HIV, HHV-8 and HCV, and special expertise in the investigation of the immunopathogenesis of HCV infection. Each of the Specialty Laboratories actively participates in the NIAID-sponsored Immunology Quality Assurance Program.

Human DNA Genomics Repository. A Human Genomics Repository located at Vanderbilt University includes specimens from nearly 8,000 patients who have participated in over 200 ACTG protocols. Patients consenting to have specimens deposited in the bank are enrolled in A5128, a protocol in which patients

consent to donation of peripheral blood for DNA extraction and repository deposition. Samples are “de-linked” from individual patient identifiers, but can be connected to demographic characteristics, therapeutic interventions, and clinical outcomes. Samples from this repository are available for investigator-initiated, hypothesis-driven studies of the role of host genetic factors in HIV pathogenesis and therapy.

F. Statistical and Data Management Center

The SDMC comprises the Statistical and Data Analysis Center (SDAC) based at the Harvard University School of Public Health (HSPH), and the Data Management Center (DMC) located in the Amherst, New York, office of Frontier Science and Technology Research Foundation (FSTRF). Dr. Michael Hughes is the PI for the SDMC. These organizations have served as the SDMC for the ACTG since 1989.

The SDMC is accountable to the ACTG and its Network Leadership through interactions with the ACTG Leadership Steering Committee and membership on the AEC. A full description of the SDMC's activities is provided in a separate application. Briefly, the SDMC provides expertise in study design and analysis that is essential for the successful conduct of clinical trials and their associated scientific research, including systems for communication among investigators. The SDMC must also provide technical expertise in methods for data transfer and management, and analytical skill for handling the enormous array of statistical problems that arise in AIDS clinical research. Because of their understanding of statistical theory and experience in clinical trials, SDAC statisticians are able to provide judgment and advice not only about specific studies, but also about overall research strategies and goals. SDAC and FSTRF maintain a high level of interaction with protocol teams, with the OPS, with the Research Agenda and Scientific Committees, and with the AEC.

III. Unique Strengths of the Network

The ACTG has a number of unique strengths and characteristics that have been critical to the execution of its research agenda. We will continue to take advantage of and build upon these strengths to carry out a focused and prioritized research plan that addresses the breadth of the critically important research questions that remain in the field of HIV/AIDS therapeutics. The ACTG has: (1) built capacity and transferred technology to conduct therapeutic research in international resource-limited settings and integrated international investigators at all levels of the structure, function, and scientific leadership of the Group; (2) developed a cadre of expert clinical and laboratory investigators capable of planning and executing the research plan articulated in this application; (3) formed a Network of clinical research sites with the investigative staff and patients representative of the demographic populations most affected by HIV/AIDS in the U.S. and in international resource-limited settings, and required to implement, enroll and complete the studies outlined in expeditious, efficient, and highly competent fashion; (4) built strong collaborative relationships with pharma, other NIAID and NIH institute-sponsored networks and investigators external to the ACTG; (5) developed the sophisticated administrative, logistical, and management tools required to efficiently and productively carry out the work planned; and (6) developed a cadre of highly innovative statistical investigators and a flexible, efficient, and effective data management system that assures the research findings published by the Network are of the highest level of excellence. We will continue to bring these attributes to bear on our ultimate goal of reducing or eliminating the morbidity and mortality associated with HIV/AIDS in our time.